REMARKS/ARGUMENTS

The Office Action mailed April 1, 2008 has been carefully reviewed. Reconsideration of this application, as amended and in view of the following remarks, is respectfully requested.

Claims 1-17 appeared in the application as originally filed. Claims 1-10 are withdrawn from consideration as a response to a restriction requirement. Claims 12-15 have been cancelled. The claims presented for examination are: claims 11, 16, and 17.

Applicants' Invention

Applicants' invention is described in the portions of Applicants' original specification quoted below and drawing FIG. 4 of Applicants' original drawings reproduced below.

> [0007] The present invention provides a method of fabricating a DNA molecule of user-defined sequence, comprising the steps of preselecting a multiplicity of DNA sequence segments that will comprise the DNA molecule of user-defined sequence, separating the DNA sequence segments temporally, and combining the multiplicity of DNA sequence segments with at least one polymerase enzyme wherein the multiplicity of DNA sequence segments join to produce the DNA molecule of user-defined sequence. The method comprising preselecting a multiplicity of DNA sequence segments that will comprise the DNA molecule using computational techniques to break the user-defined sequence into fragments of defined size, arraying the fragments of defined size into groups, and assembling the groups into double-strand DNA molecules of predetermined base-pairs to produce the DNA molecule of user-defined sequence. In one embodiment the step of separating the DNA sequence segments temporally is accomplished by the DNA sequence segments being added gradually, in sequence order. In another embodiment the step of separating the DNA sequence segments temporally is accomplished by the DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors. In another embodiment a method of fabricating a DNA molecule of user-

defined sequence comprises preselecting a multiplicity of DNA sequence segments that will comprise the DNA molecule of user-defined sequence, and combining the multiplicity of DNA sequence segments with at least one polymerase enzyme wherein the multiplicity of DNA sequence segments join to produce the DNA molecule of user-defined sequence.

[0040] Description of Another Embodiment – Applicants have previously described various embodiment of the invention comprising fabricating a DNA molecule of user-defined sequence by preselecting a multiplicity of DNA sequence segments that will comprise the DNA molecule of user-defined sequence, wherein the multiplicity of DNA sequence segments comprise n-mers, wherein n is a number less than 20, and combining the multiplicity of DNA sequence segments with at least one polymerase enzyme wherein the multiplicity of DNA sequence segments join to produce the DNA molecule of user-defined sequence. This embodiment provides an example of the polymerase-based synthesis of a user-defined DNA sequence, using pre-synthesized 8-base, single-stranded DNA molecules (8-mers) as starting substrates. For purposes of this example, when DNA is described as 40 bases long, it is presumed to be single-stranded. When DNA is described as being 40 base pairs, it is presumed to be double-stranded.

[0041] How a sequence is chosen: The DNA sequence is entirely user-defined. It can be a specific gene, human or otherwise, that one wishes to synthesize. It can also be a purely arbitrary DNA sequence, of any length. This DNA sequence will be made using very short oligonucleotides (synthetic single-stranded DNA molecules) and DNA polymerase.

[0042] Why a sequence is divided into short oligos: Once the sequence to be synthesized has been chosen, it is divided into 8-base segments, since these are the components from which the final product will be assembled. As the final DNA molecule will be double-stranded, for any given length of DNA, (e.g., 40 base pairs) the number of 8-mers necessary to synthesize it must be sufficient to produce a double-stranded molecule. Thus, rather than five 8-mers to make a 40- base-pair final product (8x5=40), the synthesis would require ten 8-mers. Once the desired molecule has been divided, the appropriate 8-mers can be gathered (from the possible 65,536 8-mers) for the subsequent polymerase-based assembly.

[0043] Why parallel synthesis is so important: There are literally billions of possible sequences resulting from combining the thousands of 8-mers necessary to make a gene-length product. If all of the component 8-mers were combined and reacted with DNA polymerase, the result would be a random collection of DNA, of innumerable different sequences, possibly

none representing the correct one. It is therefore necessary to combine the component 8-mers into smaller groups, as this is the method most likely to minimize errors while producing the maximum amount of the correct product. The groups into which the 8-mers are divided will contain highly variable numbers of 8-mers; the size of each group is dependent on the initial sequence of the desired product. To make, for example, an 800-base-pair DNA molecule requires two hundred 8-mers. These may be combined in groups of any number from two to 200, depending on the sequence of the 800-base-pair product. The standard for the groups is ten 8-mers, or enough to produce a 40-base-pair DNA molecule.

[0044] How a sequence is divided into short oligos: The desired final sequence is divided into its component 8-mers by a computer program. This program uses the thermodynamic and kinetic aspects of DNA base pairing to divide the final product into its precursor 8-mers. This program compares all of the possible hybridizations (the act of two single-stranded oligonucleotides joining by hydrogen bond-mediated base pairing to become a double-stranded DNA molecule) of the 8-mers into which the target DNA molecule has been divided. There are many opportunities for error in the synthesis process, most of which are caused by improper hybridization of 8-mers to one another. The computer program is designed to minimize these errors by combining the 8-mers into small groups that are the most likely to produce the desired product, and the least likely to produce errors.

[0045] How the short oligos are assembled into longer DNA molecules: The groups of 8-mers are combined with the necessary reagents to allow DNA polymerase-based DNA synthesis. These include the appropriate buffers and nucleotides. The specifics of this process are contained in the 4-mer embodiment. Once the 8-mers have been converted into the desired product (e.g., 40-base-pair molecules), then these 40 base-pair products are themselves combined into subsequent polymerase-mediated reactions, in combinations dictated by the computer program. In this way, the reactions progress from converting groups of ten 8-mers into 40-base-pair molecules, then converting groups of 40 base-pair molecules into longer (e.g., 200-base-pair) molecules, and then finally converting these into the final, desired product.

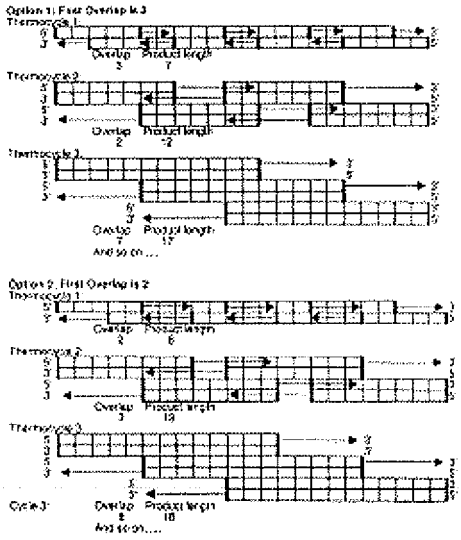


FIG.4

[0046] Section 1: Use of odd-sized starting oligos - Referring now to FIG. 4, another embodiment of a system of creating long DNA sequences, e.g., 1-10 kilobases, from short oligos of length n (n-mers) of the present invention is illustrated. The system is designated generally by the reference numeral 400. The system of parallel synthesis 400 provides a process for making very long (greater than is possible with conventional phosphoramidite chemistry) DNA of user-defined sequence. The method begins by using computational techniques to break the desired sequence into fragments of defined size.

[0047] These n-base fragments are then arrayed in groups of n-base oligonucleotides and assembled into double-strand DNA molecules using DNA polymerase. The starting oligos may be of size n, where n is an odd number. The desired, hybridizing overlaps between oligos in the first thermocycle of PCR may be specified by the user. Table 1 gives a few examples of the overlap length, oligo length, and number of polymerized bases for several scenarios of starting oligo size and overlap in the first thermocycle, and the formula for computing these variables. The products of the reactions in the first tier of PCR reactions (each PCR reaction involves many thermocycles) are then combined, in as many steps as necessary, and assembled by polymerase into still-longer molecules, until the final desired product is assembled. The final product is then amplified using PCR.

[0048] The assembly process is substantially the same as the process called DNA shuffling. It is similar to PCR in that there is a template, a primer, a DNA polymerase, and the attendant nucleotides and buffers. It is dissimilar to PCR in that the primer and template are the same entities – the n-mers themselves. Following the parallel assembly process, the final product can be

amplified by PCR. Any DNA polymerase commonly used for PCR can be used for this purpose.

[0049] The system 400 is similar to the system 300 described above and illustrated in FIG. 3; however, in the system 400, the starting oligos may be of odd length instead of even length. That is, in the system 300, the oligos, or n-mers, are of even length equal to n with a hybridizing overlap between complementary oligos of length n/2 in the first two thermocycles. In contrast, in the system 400, the length n may be odd, and the overlap length between hybridizing oligos may be specified by the user. Given a desired overlap v_1 in the first thermocycle and the length n of the starting oligos that are specified by the user, the length l_c of oligonucleotides starting thermocycle c is computed by the formula: $l_c=n(c-1)+p_1$ for $c>1$, where $p_1=n-v_1$. The length v_c of desired overlap between oligos in thermocycle c is given by $v_c=n(c-2)+p_1$ for $c>1$. The number p_c of bases polymerized in thermocycle c is $p_c= n$ for $c>1$.

[0050] Figure 4 illustrates the first three thermocycles for the two scenarios starting with n=5 outlined in Table 1 below. Each yellow box indicates a nucleotide, and a series of yellow boxes represents an oligonucleotide, where the heavy black vertical lines indicate the ends of an oligonucleotide. The 5′ and 3′ ends of the plus and minus strands are labeled, and where nucleotides are in the same column (overlap vertically) and in the right orientation (5′ to 3′ on the top strand, and 3′ to 5′ on the bottom, from left to right), the desired hybridization occurs. Red arrows indicate polymerization (both the direction and the number of polymerized bases) from 3′ ends during the specified thermocycle. In the first case, in which the first overlap $v_1=3$, polymerization extends each oligonucleotide by $p_1=2$ bases, and the length of the oligonucleotides starting the second thermocycle is 7 bases. In the second case, the first overlap $v_1=2$, polymerization extends each oligonucleotide by $p_1=3$ bases, and the length of the oligonucleotides starting the second thermocycle is 8 bases. These are merely two examples, and any other values of n and v_1 specified by the user may be used.

35 U.S.C. § 112 Rejection

In numbered paragraph 4 of the Office Action mailed April 1, 2008, claim 16 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action mailed April 1, 2008 stated:

> "Claim 16 recites the limitation 'said starting oligos of length n-mers' in line. There is insufficient antecedent basis for this limitation in the claim."

Applicants have amended claim 16 to provide an antecedent basis for the limitation in order to overcome the rejection in the Office Action mailed April 1, 2008. Applicants believe that the amendment overcomes the rejection of claim 16 under 35 U.S.C. § 112, second paragraph, and that a complete response to the rejection has been provided.

35 U.S.C. § 102(e) Rejection Claims 11 and 13-15 – Evans Reference

In numbered paragraph 6 of the Office Action mailed April 1, 2008, claim 11 was rejected under 35 U.S.C. § 102(e) as being anticipated by the Evans U. S. Published Patent Application No. 2003/0087238 (hereinafter "Evans").

Applicants disagree with the following statements in the Office Action mailed April 1, 2008:

> "Regarding claim 11 Evans discloses ....
>
> (c) assembling the groups *in vitro* into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (paragraphs 58 and 68 teach assembly using a polymerase; paragraphs 38, 93-98, and 195-199 teach assembly by PCR, which inherently comprises parallel synthesis and shuffling using a DNA polymerase)
>
> wherein the step of separating the DNA sequence segments occurs temporally (see paragraphs 58 and 62) and the step of assembling the groups into double-stranded DNA molecules of pre-determined base pairs is accomplished by adding the DNA sequence segments gradually, in sequence order (paragraphs 58 and 62).
>
> Further regarding claim 11, Evans teaches that the sequential addition minimizes errors (paragraph 66) and that computational techniques may be use to optimize (i.e. minimize errors) in the

> entire method (paragraph 178). Evans further teaches that the resulting polynucleotide is 5 kb (paragraph 53), which anticipates the claimed size range of 1-10 kb. Evans also teaches that the oligos used in the method have a length n, which is an odd number (paragraphs 58 & 82)'

The Evans reference does not show "assembling the groups *in vitro* into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling," or "adding the DNA sequence segments gradually, in sequence order" or "computational techniques may be use to optimize (i.e. minimize errors)" or "the oligos used in the method have a length n, which is an odd number."

Applicant points out that that a number of elements of Applicants' claim 11 are not found in the Evans reference. For example, the following elements of Applicants' claim 11 are not found in the Evans reference:

> "assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or
>
> "wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number."

The standard for a 35 U.S.C. § 102 rejection is stated in *RCA Corp. v. Applied Digital Systems, Inc.*, 221PQ 385, 388 (d. Cir. 1984) "Anticipation is established only when a single prior art reference discloses, either expressly or under principles of inherency, each and every element of a claimed invention." Since the claim elements identified above are not found in the Evans reference,

the Evans reference does not support a 35 U.S.C. § 102(e) rejection of Applicants' claim 11 and the rejection should be withdrawn.

35 U.S.C. § 102(a) & 102(e) Rejection Claims 16 and 17 – Evans Reference

In numbered paragraph 7 of the Office Action mailed April 1, 2008, claims 16 and 17 were rejected under 35 U.S.C. § 102(a) and 102(e) as being anticipated by Evans.

Applicants disagree with the following statements in the Office Action mailed April 1, 2008:

> "Regarding claim 11 Evans discloses ....
>
> (c) assembling the groups *in vitro* into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (paragraphs 58 and 68 teach assembly using a polymerase; paragraphs 38, 93-98, and 195-199 teach assembly by PCR, which inherently comprises parallel synthesis and shuffling using a DNA polymerase)
>
> wherein the step of separating the DNA sequence segments occurs temporally (see paragraphs 58 and 62) and the step of assembling the groups into double-stranded DNA molecules of pre-determined base pairs is accomplished by adding the DNA sequence segments gradually, in sequence order (paragraphs 58 and 62).
>
> Further regarding claim 11, Evans teaches that the sequential addition minimizes errors (paragraph 66) and that computational techniques may be use to optimize (i.e. minimize errors) in the entire method (paragraph 178). Evans further teaches that the resulting polynucleotide is 5 kb (paragraph 53), which anticipates the claimed size range of 1-10 kb. Evans also teaches that the oligos used in the method have a length n, which is an odd number (paragraphs 58 & 82)"
>
> "Regarding claim 16 , Evans teaches that the oligonucleoti[des] may be different lengths (paragraph 53). Evans further teaches

examples of oligonucleotides with lengths of 15 (n), 16 (n+l), 17 (n+2), etc (see paragraph 53)."

"Regarding claim 17, Evans teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Evans teaches variation of the oligo length and overlap between the fragments (paragraphs 53 and 54). These DNA fragments inherently comprise multiple reading frames."

The Evans reference does not show "assembling the groups *in vitro* into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling," or "adding the DNA sequence segments gradually, in sequence order" or "computational techniques may be use to optimize (i.e. minimize errors)" or "the oligos used in the method have a length n, which is an odd number" or "oligonucleotides with lengths of 15 (n), 16 (n+l), 17 (n+2)" or "multiple reading frames."

Applicant points out that that a number of elements of Applicants' claims 16 and 17 are not found in the Evans reference. For example, the following elements of Applicants' claims 16 and 17 are not found in the Evans reference:

Parent Claim 11
"assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or

Parent Claim 11
"wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number."

Claim 16
"wherein said starting oligos of length n (n-mers) where n is an odd number are starting oligos of length n+1 or n+2."

Claim 17
"wherein said multiplicity of DNA sequence segments comprise oligos in multiple reading frames."

The standard for a 35 U.S.C. § 102 rejection is stated in *RCA Corp. v. Applied Digital Systems, Inc.*, 221PQ 385, 388 (d. Cir. 1984) "Anticipation is established only when a single prior art reference discloses, either expressly or under principles of inherency, each and every element of a claimed invention." Since the claim elements identified above are not found in the Evans reference, the Evans reference does not support a 35 U.S.C. § 102(a) or 35 U.S.C. § 102(e) rejection of Applicants' claims 16 and 17and the rejection should be withdrawn.

35 U.S.C. § 103 Rejection - Selifonov & Evans

In numbered paragraph 9 of the Office Action mailed April 1, 2008, claims 11 and 17 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Selifonov International Patent Application No. WO 00/42560 (hereinafter "Selifonov") in view of Evans.

The rejection of claims 11 and 17 under 35 U.S.C. § 103(a) is respectfully traversed. Applicants' claimed invention is a specific combination of steps specified in claims 11 and 17. The Office Action mailed April 1, 2008 points to multiple isolated portions of the specifications of the Selifonov and Evans references that motion isolated language and concepts similar to language and concepts of Applicants' claims 11 and 17; however neither the Selifonov reference or the Evans reference shows or suggests the specific combination of steps specified in Applicants' claims 11 and 17.

Prima Facie Case of Obviousness Has Not Been Established

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) include, "Ascertaining the differences between the prior art and the claims at issue." The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness. The prior art reference (or reference when combined) must teach or suggest all the claim limitations. There must be a reasonable expectation of success with the proposed combination. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

Disagreement With Statements in Office Action

As stated above Applicants disagree following statements in the Office Action mailed April 1, 2008 regarding the Evans reference. Applicants disagree with the following statements in the Office Action mailed April 1, 2008 regarding the Selifonov reference:

> "Regarding claim II, Selifonov discloses a method of producing a DNA molecule of user-defined sequence comprising:
>
> virtually preselecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into virtual fragments of length n (n-mers), where n is an odd number (page 14, lines 20-29 and page 21, lines 12-22 teach using computational methods to virtually break the DNA molecule into virtual fragments; page 6, lines 8-10 teach using n-mers where n is an odd number)
>
> providing fragments of length n (n-mers) of defined size, where n is an odd number, that correspond to the virtual fragments (page 9, lines 23-31 and

page 21, lines 12-30 teach providing fragments *in vitro* that correspond to the virtual fragments generated in step (a) above; page 6, lines 8-10 teaches using n-mers where n is an odd number in the synthesis method)

arraying the fragments of defined size into groups (page 14, lines 27-30, where Selifonov teaches that the fragments may be left with the parental strands or transferred to a new population. Selifonov also teaches formation of new populations; see also page 21, lines 14-15 and lines 23-30, where sets are combined)

separating the DNA sequence segments temporally (page 22, lines 4-19, where Selifonov teaches variation of the composition of fragments in the recombination reaction and/or performing multiple recombination reactions. This is a temporal separation of the DNA segments)

assembling the groups into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (page 21, line 23 - page 22, line 13).

See also Figures 4A-D *for a* flow-chart depiction of the method of Selifonov.
Further regarding claim 11, Selifonov teaches that the assembled polynucleotide of user-defined sequence is 1.6 kb (page 70), a value within the claimed range of 1-10 kb. Selifonov also teaches computational modeling in an effort to minimize reassembly errors (see for example, page 10, lines 26-33). However, Selifonov does not explicitly teach sequential addition of DNA segments in the reassembly process.

Regarding claim 17, Selifonov teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Selifonov teaches variation of the oligo length and overlap between the fragments (page 33, lines 1-6). These DNA fragments inherently comprise multiple reading frames.

References Do Not Teach All Claim Limitations

The criteria that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. The Selifonov reference and Evans reference do not disclose a number of Applicants' claim

limitations. The Selifonov reference and the Evans reference do not disclose the limitations of Applicants' claims 11 and 17 identified below.

> "assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or
>
> "wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number," or
>
> "wherein said multiplicity of DNA sequence segments comprise oligos in multiple reading frames."

Since the limitations listed and described above are not shown by the Selifonov reference or the Evans reference, a *prima facie* case of obviousness has not been established. Further, since the Selifonov reference and the Evans reference fail to show the claim limitations of Applicants' claims 11 and 17 there can be no combination of the two references that would show Applicants' invention. There is no combination of the Selifonov reference and the Evans reference that would produce the combination of elements of Applicants' claims 11 and 17. Thus, the combination of references in the Office Action mailed April 1, 2008 fails to support a rejection of claims 11 and 17 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

Teaching-Suggestion-Motivation (TSM) Test

The Office Action mailed April 1, 2008 does not meet the teaching-suggestion-motivation (TSM) test. The TSM test is "whether there is something in the prior art to suggest the desirability, and thus the obvious nature, of the

combination of the references." The Office Action mailed April 1, 2008 does not point to anything in the prior art to suggest the desirability, and thus the obvious nature, of the combination of the references. Further there are no "other "reasons" for combining the Selifonov reference and the Evans reference.

The Selifonov reference describes "genetic algorithms." The Evans reference describes "polynucleotide encoding a target polypeptide." There would be no reason for combining the Selifonov reference and the Evans reference and the Office Action mailed April 1, 2008 does not point to anything in the prior art to suggest the combination of the Selifonov reference and the Evans reference.

Thus, the combination of references in the Office Action mailed April 1, 2008 fails to support a rejection of claims 11 and 17 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

No Reasons for Combining Selifonov and Evans

The criteria that the Examiner must provide reasons for combining the references has not been established. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The rejection in the Office Action mailed April 1, 2008 does not provide an explanation of how or why the Selifonov reference and the Evans reference would be combined.

The Selifonov reference and the Evans reference do not recognize the problem solved by Applicant's claimed invention. The Selifonov reference and the Evans reference fail to disclose the benefits of Applicants claimed invention. Thus, the combination of references in the Office Action mailed April 1, 2008 fails

to support a rejection of claims 11 and 17 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

No Reasonable Expectation of Success

The Office Action mailed April 1, 2008 does not established "a reasonable expectation of success in combining the references." The references are so dissimilar there would not be a reasonable expectation of success in combining the references.

The Selifonov reference describes "genetic algorithms." The Evans reference describes "polynucleotide encoding a target polypeptide." There would be no reason for combining the Selifonov reference and the Evans reference. There is no expectation of success in combining Selifonov and Evans. Thus, the rejection should be withdrawn.

35 U.S.C. § 103 Rejection - Selifonov and Evans

In numbered paragraph 10 of the Office Action mailed April 1, 2008, claim 16 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Selifonov in view of Evans and further in view of Murphy et al U. S. Patent No. 6,994,963 (hereinafter "Murphy").

The rejection of claim 16 under 35 U.S.C. § 103(a) is respectfully traversed. Applicants' claimed invention is a specific combination of steps specified in claim 16. The Office Action mailed April 1, 2008 points to multiple isolated portions of the specifications of the Selifonov and Evans and Murphy references that motion isolated language and concepts similar to language and concepts of Applicants' claim 16; however neither the Selifonov reference or the Evans reference or the Murphy shows or suggests the specific combination of steps specified in Applicants' claim 16.

Prima Facie Case of Obviousness Has Not Been Established

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) include, "Ascertaining the differences between the prior art and the claims at issue." The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness. The prior art reference (or reference when combined) must teach or suggest all the claim limitations. There must be a reasonable expectation of success with the proposed combination. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

Disagreement With Statements in Office Action

As stated above Applicants disagree following statements in the Office Action mailed April 1, 2008 regarding the Evans and Selifonov references. Applicants disagree with the following statements in the Office Action mailed April 1, 2008 "The combined teachings of Selifonov and Evans result in the method of Claims 11 and 17."

References Do Not Teach All Claim Limitations

The criteria that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. The Selifonov reference and Evans reference and Murphy reference do not disclose a number of Applicants' claim limitations. The Selifonov reference and the Evans reference and Murphy reference do not disclose the limitations of Applicants' claim 16 identified below.

"assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or

"wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number," or

"wherein said starting oligos of length n (n-mers) where n is an odd number are starting oligos of length n+1, or n+2."

Since the limitations listed and described above are not shown by the Selifonov reference or the Evans reference or the Murphy reference, a *prima facie* case of obviousness has not been established. Further, since the Selifonov reference and the Evans reference and the Murphy reference fail to show the claim limitations of Applicants' claim 16 there can be no combination of the three references that would show Applicants' invention. There is no combination of the Selifonov reference and the Evans reference and the Murphy reference that would produce the combination of elements of Applicants' claim 16. Thus, the combination of references in the Office Action mailed April 1, 2008 fails to support a rejection of claim 16 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

Teaching-Suggestion-Motivation (TSM) Test

The Office Action mailed April 1, 2008 does not meet the teaching-suggestion-motivation (TSM) test. The TSM test is "whether there is something in the prior art to suggest the desirability, and thus the obvious nature, of the combination of the references." The Office Action mailed April 1, 2008 does not

point to anything in the prior art to suggest the desirability, and thus the obvious nature, of the combination of the references. Further there are no "other "reasons" for combining the Selifonov reference and the Evans reference.

The Selifonov reference describes "genetic algorithms." The Evans reference describes "polynucleotide encoding a target polypeptide." There would be no reason for combining the Selifonov reference and the Evans reference and the Office Action mailed April 1, 2008 does not point to anything in the prior art to suggest the combination of the Selifonov reference and the Evans reference.

Thus, the combination of references in the Office Action mailed April 1, 2008 fails to support a rejection of claim 16 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

No Reasons for Combining Selifonov and Evans and Murphy

The criteria that the Examiner must provide reasons for combining the references has not been established. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The rejection in the Office Action mailed April 1, 2008 does not provide an explanation of how or why the Selifonov reference and the Evans reference and the Murphy reference would be combined.

The Selifonov reference and the Evans reference and the Murphy reference do not recognize the problem solved by Applicant's claimed invention. The Selifonov reference and the Evans reference fail to disclose the benefits of Applicants claimed invention. Thus, the combination of references in the Office

Action mailed April 1, 2008 fails to support a rejection of claim 16 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

No Reasonable Expectation of Success

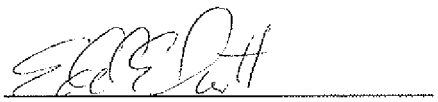
The Office Action mailed April 1, 2008 does not established "a reasonable expectation of success in combining the references." The references are so dissimilar there would not be a reasonable expectation of success in combining the references.

The Selifonov reference describes "genetic algorithms." The Evans reference describes "polynucleotide encoding a target polypeptide." The Murphy reference describes "generating a pool of nucleic acid fragments." There would be no reason for combining the Selifonov reference and the Evans reference and the Murphy reference. There is no expectation of success in combining Selifonov and Evans and Murphy. Thus, the rejection should be withdrawn.

SUMMARY

The undersigned respectfully submits that, in view of the foregoing amendments and the foregoing remarks, the rejections of the claims raised in the Office Action dated April 1, 2008 have been fully addressed and overcome, and the present application is believed to be in condition for allowance. It is respectfully requested that this application be reconsidered, that the claims be allowed, and that this case be passed to issue. If it is believed that a telephone conversation would expedite the prosecution of the present application, or clarify matters with regard to its allowance, the Examiner is invited to call the undersigned attorney at (925) 424-6897.

Respectfully submitted,



Eddie E. Scott
Attorney for Applicant
Registration No. 25,220
Tel. No. (925) 424-6897

Livermore, California
Dated: June 27, 2008